DOI:
10.1016/S2215-0366(15)00317-X

Document Version
Peer reviewed version

Title: The PACE trial of rehabilitative treatments for chronic fatigue syndrome: long-term outcomes.

Authors: Michael Sharpe MD[1*$], Kimberley A. Goldsmith PhD[2*], Anthony L. Johnson PhD[3$], Trudie Chalder PhD[4$], Jane Walker PhD[1] and Peter D. White MD[5$]

Affiliations:

[1]Psychological Medicine Research, University of Oxford Department of Psychiatry, Oxford, UK

[2]Department of Biostatistics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[3]Medical Research Council Clinical Trials Unit at UCL, London, UK

[4]Academic Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, London, UK

[5]Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Bart's and The London Medical School, Queen Mary University, London, UK

Corresponding author:

Michael Sharpe, Psychological Medicine Research, University of Oxford Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK

Telephone: +44(0)1865 226 397

Email: michael.sharpe@psych.ox.ac.uk

***Joint first authorship**

[$]Full professors

SUMMARY

Background

The PACE trial of treatments for chronic fatigue syndrome (CFS) found that, when added to specialist medical care (SMC), cognitive behaviour therapy (CBT) and graded exercise therapy (GET) were superior to adaptive pacing therapy (APT) and to SMC alone, in improving fatigue and physical functioning one year after randomisation. The aim of this paper is to report the long-term (more than two year) outcomes of trial participants including: (a) additional treatments received by patients after completing the trial; (b) changes in outcomes within the original randomised treatment groups; (c) differences in outcome between these treatment groups.

Methods

Postal questionnaire survey measuring primary (fatigue and physical functioning) and selected secondary trial outcome measures sent to the 604 of the original 641 participants who had not withdrawn from follow-up.

Findings

The median time from randomisation to long-term follow-up was 31 months (range 24 to 53 months). We obtained usable data on 481 of 604 eligible participants (80%). Nearly half of participants received treatment after the trial. The benefits of CBT and GET seen in the trial were maintained. Further improvements were observed in those originally allocated to CBT, SMC, and APT but not GET. The only difference between original treatment groups at follow up was better physical functioning in those allocated to CBT compared with APT (6.4, 95% CI 0.4 to 12.4, p = 0.035).

Interpretation

The beneficial effects of CBT and GET on fatigue and physical functioning are maintained at long-term follow-up.

Funding

UK Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions, National Institute for Health Research (NIHR), NIHR Biomedical

Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust, and King's College London.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by chronic disabling fatigue in the absence of an alternative diagnosis. Myalgic encephalomyelitis (ME) is thought by some to be the same disorder and by others to be different. The prevalence of CFS is between 0.2% and 2.6% worldwide [1]. If untreated the prognosis for recovery is poor [2].

We previously carried out a multi-centre randomised trial (PACE: Pacing, graded Activity and Cognitive behaviour therapy: a randomised Evaluation) to compare the most commonly used non-pharmacological treatments for CFS [3]. When we planned the trial there was some evidence that cognitive behaviour therapy (CBT) and graded exercise therapy (GET) could improve patient outcomes. However, these rehabilitative treatments were controversial amongst patient organizations and adaptive pacing therapy (APT) and specialist medical care (SMC) were regarded as better alternatives. The PACE trial aimed to compare the outcomes of patients who were randomly allocated to one of the following four treatments: SMC alone, or SMC plus APT, CBT, or GET. The trial found that at the final one year (52 week) follow-up, patients who had received CBT or GET had significantly greater improvements in their fatigue and physical functioning than those who had received either APT or SMC alone.

Whilst the benefits of CBT and GET seen at one year are encouraging it is clearly also important to know whether patients continue to experience these benefits over a longer period of time. As there have been few previous long-term follow-up studies of participants in trials of treatments for CFS [4-8] we conducted a long-term follow-up study of the PACE trial participants. The aims of this follow-up study were to: (a) describe the additional therapy (APT, CBT, GET) that participants received after the 12 month (52 week) final trial outcome assessment; (b) compare the outcomes of participants within each randomised treatment group at follow-up with the final trial outcome assessment; (c)

compare the long-term outcomes between the original randomised trial treatment groups, bearing in mind the limitations on interpretation imposed by the provision of additional, non-randomly allocated therapy during the follow-up period.

METHODS

The PACE trial

The PACE trial methods, including details of the trial treatments, are described in full in the main trial protocol and report [9 3]. In summary, this was a four-arm parallel group randomised controlled trial of non-pharmacological treatments for patients meeting the Oxford criteria for CFS, which require fatigue to be the patient's principal symptom [10]. 641 participants were recruited from six secondary care clinics in the United Kingdom and were randomly allocated to SMC alone, or SMC plus APT, CBT, or GET. Participants received the therapies (APT, CBT, and GET) in one-to-one sessions (maximum 14 sessions) during the first six months of trial participation, with an additional booster session offered at nine months. The trial primary outcome measures were fatigue and physical functioning, measured using self-report scales, at participants' final trial outcome assessment 12 months (52 weeks) post-randomisation.

Additional therapy given after the trial

After completing their final trial outcome assessment one year after randomisation, PACE trial participants were offered additional therapy if they were still unwell, they wanted more treatment, and their PACE trial doctor agreed this was appropriate. The choice of type of treatment offered (APT, CBT, or GET) was made by the patient's doctor taking into account both the patient's preference and their own opinion of which would be most beneficial. These choices were made before the overall trial findings were known.

Participants in the long-term follow-up study

We obtained consent from the 641 PACE trial participants to contact them for a long-term follow-up assessment at the time of trial enrolment. 19 (3%) participants withdrew consent for further data collection and 622 were therefore eligible to take part in the follow-up study.

Ethical approval

Ethical approval for the trial and follow-up study was given by the West Midlands Multi-centre Research Ethics Committee (MREC 02/7/89).

Procedure

Follow-up assessments were conducted using a brief postal questionnaire. The trial had recruited between March 2005 and November 2008. The follow up questionnaires were mailed to eligible participants from January 2008 and were timed to be *at least* two years after the date of their randomisation.

Measures

The follow-up questionnaire included the following: (a) questions about the additional therapies that participants had received for CFS since their final trial outcome assessment; (b) severity of fatigue using the Chalder Fatigue Questionnaire (CFQ) [11]; (c) physical functioning using the SF-36 physical functioning subscale (SF-36PF) [12]; (d) overall change in perceived health since trial enrolment using the participant-rated clinical global impression of change score (PCGI) a seven-point scale rated from 'very much worse' to 'very much better'[13]; (e) impairment of daily activities using the participant-rated work and social adjustment scale (WSAS) scored in five domains, each rated 0 to 8, producing an overall score of 0 to 40, with lower scores indicating less impairment [14].

We included the CFQ and the SF-36PF in the follow-up questionnaire because these were the primary outcome measures used in the PACE trial. We chose two of the secondary trial outcome measures (PCGI and WSAS) in order to enhance our estimate of patient well-being whilst keeping the questionnaire sufficiently short to ensure a good response rate.

Analysis

The variables to be analysed were first summarized using means and standard deviations, median and quartiles, or frequencies and proportions, as appropriate.

We compared the proportions of eligible participants who returned follow-up questionnaires across the randomised treatment groups (SMC alone, SMC with APT, CBT, or GET) using Fisher's exact test. We also compared the (pre-randomisation) baseline characteristics of PACE trial participants who did and did not take part in the follow-up study using Fisher's exact test, independent samples t-tests, or the Mann-Whitney U test as appropriate. Baseline characteristics of participants in the subset who took part in the follow-up study were compared across original randomised treatment groups using Fisher's exact test, ANOVA, or the Kruskal-Wallis test as appropriate.

Differences between the original randomised treatment groups in the proportion of patients who received additional treatment after their final trial outcome assessment were compared using Fisher's exact test, and in the number of additional treatment sessions by the Kruskal-Wallis test.

We calculated differences in outcomes between the final trial assessment and long-term follow-up *within* each original treatment group using paired samples t-tests for fatigue (CFQ), physical functioning (SF-36PF), impairment of daily activities (WSAS), and the exact McNemar test for overall change in health (PCGI). We also calculated differences in trial outcomes for those with and without long-term follow-up data, using independent samples t-tests.

We constructed profile plots of fatigue (CFQ) and physical functioning (SF-36 PF) for follow-up study participants in each randomised treatment group, including data from baseline, 12 week, 24 weeks, and final one year (52 week) trial outcome assessments, and the long-term follow-up assessment.

We assessed the differences in the measured outcomes *between* the original randomised treatment groups using linear mixed effects regression models with random intercepts and slopes for participants during trial participation and at long-term follow-up. We included the following covariates in the models: treatment group, trial stratification variables (trial centre and whether participants met the International CFS criteria[15], London ME criteria [16], and DSMIV depressive disorder criteria) [17, 18], time, time by treatment group interaction term, long-term follow-up data by

treatment group interaction term, baseline values of the outcome, and missing data predictors (gender, education level, Body Mass Index, and patient self-help organization membership), so the differences between groups obtained were adjusted for these variables. We calculated differences between treatment groups on overall change in perceived health (PCGI) using a binary logistic generalized estimating equation model with an exchangeable working correlation and bootstrapped standard errors, and with similar covariates to those used in the models for the other outcomes. Finally we compared the proportion of participants in each treatment group who had a clinically useful difference (CUD) in fatigue (CFQ) and physical functioning (SF-36) scores between trial enrolment (baseline) and long-term follow-up. CUD was defined in the same way as in the PACE trial analysis [3] as 0.5 of the standard deviation (SD) of the measure in the whole sample at baseline (2 points for fatigue and 8 for physical functioning) and was compared between groups using the independent sample test for the difference between two proportions.

Role of the funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MS, KG, AJ, TC and PW had full access to data collected for the study and all authors had final responsibility for the decision to submit the report for publication.

RESULTS

The long-term follow-up sample

We sent questionnaires to the 604 of the 622 patients who had consented to long-term follow-up for whom we had current contact details. Of these 481/604 (80%) returned usable questionnaires and were included in the analysis (Figure 1). The median (quartile) time from randomisation to long-term follow-up assessment was 31 (30, 32) months with a range of 24 to 53 months. There were no differences between original randomised treatment groups in the proportions of participants who returned questionnaires (p=0.37).

[Figure 1 here]

Table 1 shows the baseline characteristics of trial participants who did and did not take part in the follow-up study. The only significant difference between these two groups was that participants who were members of an ME/CFS patient organization were more likely to take part in the follow-up study.

[Table 1 here]

Within the follow-up study sample there were no significant imbalances between randomised treatment groups in baseline characteristics (Web Appendix, Table A).

Additional treatment received after the trial

Nearly half of all the follow-up study participants received additional trial treatments after their final trial outcome assessment (Table 2). More detail is given in Web Appendix Table B. The number of participants who received additional treatments differed between the treatment groups: participants allocated to SMC were most likely to receive additional treatment (63%), followed by those allocated to APT 60/120 (50%), then GET 41/127 (32%), and CBT 36/119 (31%).

In the trial analysis plan we defined an adequate number of sessions as 10 out of a maximum possible of 15. Although a large number of the participants in the follow-up study had received additional treatment, only a minority of these had received an adequate amount as defined for the trial. Most of the additional treatment that was given in an adequate amount was either CBT or GET.

[Table 2 here]

Outcomes *within* randomised treatment groups at long-term follow-up

The long-term outcomes of participants within each randomised treatment group are shown in Figure 2 and Table 3. The improvements in both fatigue and physical functioning that had been reported by participants allocated to CBT or GET at their final trial outcome assessment were sustained (and had continued to improve in the CBT group). The improvements in the secondary measure of impairment in daily activities and in perceived health change were also sustained.

Participants originally allocated to APT reported further improvements in fatigue, physical functioning, and impairment in daily activities from final trial outcome assessment to long-term follow-up, as did those allocated to SMC alone (who also reported further improvements in perceived health change).

[Figure 2 here]

[Table 3 here]

Differences *between* randomised treatment groups at long-term follow-up

The models used in the analysis adjusting for covariates and repeated measures over time indicated that there were no significant differences between the randomised treatment groups in mean fatigue scores at long-term follow-up (Web appendix, Table C). However physical functioning was

still significantly better for those allocated to CBT when compared with those allocated to APT (p=0.035). There were also no significant differences between originally randomised groups in impairment in daily activities or in perceived health change.

Applying the criteria used in the original trial analysis plan to define a clinically useful difference (CUD) in both fatigue and physical functioning, improvements from baseline to long-term follow-up were observed in 64/118 (54%) of those originally allocated to APT, compared with 79/119 (66%) for CBT, 79/127 (62%) for GET, and 65/115 (57%) for SMC; the only difference close to reaching significance was that between CBT and APT (p=0.056).

DISCUSSION

Main findings

The main finding of this long-term follow-up study of the PACE trial participants is that the beneficial effects of the rehabilitative CBT and GET therapies on fatigue and physical functioning observed at the final one year outcome were maintained at long-term follow-up, an average of a year and a half later.

In interpreting the outcome data it is important to note that many of the participants in this follow-up study had received additional treatment for CFS after the final trial outcome assessment; the choice of whether to give each participant additional treatments, and if so which, was made by the patient's PACE trial doctor in consultation with the patient. We found that participants originally allocated to SMC in the trial were the most likely to receive additional treatment, followed by those who had APT; those originally allocated to the rehabilitative therapies (CBT and GET) were less likely to receive additional treatment. In so far as the need to seek additional treatment is a marker of continuing illness, these findings support the superiority of CBT and GET as treatments for CFS.

Participants originally allocated to SMC alone or to APT substantially improved between their final trial outcome assessment and the long-term follow-up. Whilst this improvement may have been due to many factors including the passage of time, regression to the mean, and long-term benefits of the treatment received in the trial, the observation that approximately one quarter and one third of the participants originally allocated to APT and SMC respectively had received a therapeutically adequate amount (10 or more sessions) of CBT or GET *after* the trial final trial outcome, makes it likely that this additional treatment was important in improving the long-term outcome for these patients.

There was little evidence of deterioration (negative change) in the participant rated clinical global impression change scale (PCGI) in the whole sample at long term follow-up and importantly there were no significant differences in deterioration rates between the originally allocated treatment groups. This finding suggests that none of the trial therapies are associated with long-term deterioration.

When outcomes were compared *between* the originally randomised groups, few differences were seen. This convergence in outcomes reflects the observed improvement in those originally allocated to SMC and APT, the possible reasons for which are listed above.

Previous studies

There have been a number of previously published naturalistic follow-up studies of the outcome of patients with CFS. A systematic review found 14 studies of subjects meeting operational criteria for CFS with a variety of follow-up durations and outcome measures and concluded that the prognosis was generally poor; improvement was reported by a median of 40% of participants and recovery by only 7% [2]. There have also been several small follow-up studies of patients who have received specific treatment, almost all CBT: a four-year follow-up of a small case series found that most of the patients had maintained their improvement [19]. A five -year follow-up of a small randomised trial of adults receiving CBT found persisting improvement [4]. Similar sustained improvements were found after CBT in a two-year follow-up of adolescents [5], a two year follow-up of family focused CBT in adolescents [7], and a 2.7 year follow-up of adolescents treated in a trial comparing internet delivered CBT with usual care [8]. There has however been no follow-up study of GET, although a two-year follow-up of a randomised trial of an educational intervention which included advice on graded activity found the benefits were maintained [6]. There are also no published follow-up studies of treatment with APT.

Our findings confirm reports indicating that improvements from

CBT are maintained in the long-term. A new finding is that long-term benefit also occurs following GET.

Limitations

This follow-up study has a number of limitations. First, the response rate was incomplete; there may have been some selection bias in those who returned follow-up questionnaires that led to an underestimate of the actual differences between the groups. Second, there was variation in the duration of follow-up. Third, the outcomes were self-rated and therefore potentially subject to bias. Finally, the supplementation of the originally randomly allocated treatment with additional treatment after the trial final outcome limits the conclusions that can be drawn from the between group comparisons.

Conclusion

We can conclude that the benefits of CBT and GET for patients with CFS are maintained at long-term (two and a half year) follow-up. We can also confirm that there was no evidence of deterioration in overall health from the trial final outcome assessment to follow up after any trial treatment. We note however that in all of the originally randomised treatment groups some patients remain unwell at long-term follow-up, an observation that reminds us that better treatments are still needed for those patients.

CONTRIBUTORS

The PACE trial co-principal investigators were PDW, TC and MS. MS, PDW TC and ALJ conceived and designed the follow up study. KAG and ALJ designed and did the statistical analysis. The manuscript was written by MS, KG and JW. All authors contributed to the final manuscript.

DECLARATION OF INTERESTS

PDW has done voluntary and paid consultancy word for the UK government and a reinsurance company. TC has received royalties from Sheldon Press and Constable and Robinson. MS has received royalties from Oxford University Press. KAG and JW declare no competing interests

ACKNOWLEDGEMENTS

Funding for the PACE trial was provided by the Medical Research Council, Department of Health for England, The Scottish Chief Scientist Office, and the Department for Work and Pensions. TC and KG were in part supported by the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience, Kings College London. KG was also funded by an NIHR Doctoral Fellowship. JW is in part supported by the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford NHS Foundation Trust (the views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health).

We gratefully acknowledge the help of the PACE Trial Management Group, which consisted of the authors of this paper plus (in alphabetical order): B.Angus, H. Baber, J. Bavinton, M. Burgess, L. V. Clark, D. L. Cox, J. C. DeCesare, E. Feldman, P. McCrone, G. Murphy, M. Murphy, H. O'Dowd, T. Peto,

L. Potts, R. Walwyn, and D. Wilks and the King's Clinical Trials Unit. We thank Hannah Baber for facilitating the long-term follow-up data collection.

PANEL: RESEARCH IN CONTEXT

Evidence before this study

For the original adaptive Pacing, graded Activity and Cognitive behaviour therapy; a randomised Evaluation (PACE) trial report, PubMed and Cochrane Library databases were searched to Nov 6th, 2010. The findings of this systematic review are shown in the 'Research in Context' panel of that publication. The review concluded that the untreated outcome for patients with chronic fatigue syndrome (CFS) was poor, and that there was some evidence that cognitive behaviour therapy (CBT) and graded exercise therapy (GET) improved this [3.] The PACE trial confirmed that CBT and GET were more effective than specialist medical care alone (SMC) in improving fatigue and functioning one year after randomisation but that adaptive pacing (APT) was not [3.] For this study we searched PubMed to February 1st, 2015 for follow up studies of more than one year of patients who had received a PACE trial treatment. The reports identified were small studies and almost all of patients who had received CBT. They suggested that the benefits from CBT are maintained [19 4 5 8]. We did not find any long-term follow-up study after GET (although a single follow up of an educational intervention which included advice on graded activity found the benefits were maintained [6]) or APT.

Added value of this study

Our long-term follow up of the PACE trail participants adds to what we already knew by providing robust evidence that the improvements in fatigue and function observed with CBT and GET are maintained in the longer-term (a mean of two and a half years from randomisation). It does not provide evidence that CBT and GET are better than SMC and APT in the longer term, as patients allocated to these treatment had improved to a similar degree by the time of the follow up, but the interpretation of this finding is complicated by the fact that many of these patients had received CBT or GET between the end of the trial and the long–term follow up. Importantly there was no significant worsening in perceived health during the follow up period after any of the trial treatments.

Implications of all the available evidence

Taken together the available evidence confirms that the rehabilitative treatments of CBT and GET for CFS are associated with long term improvement in fatigue and functioning for patients with CFS. However, the observation that some patients remain unwell at long-term follow-up reminds us that more effective treatments are still needed for these patients.

REFERENCES

1. Prins JB, Van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet*. 2006; **367**: 346-55.
2. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. *OccupMed (Lond)*. 2005; **55**: 20-31.
3. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011; **377**: 823-36.
4. Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry*. 2001; **158**: 2038-42.
5. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomised, controlled trial. *Pediatrics*. 2008; **121**: e619-e25.
6. Powell P, Bentall RP, Nye FJ, Edwards RH. Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. *Br J Psych*. 2004; **184**: 142-6.
7. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: Long-term follow-up of an RCT. *Behav Res Ther*. 2012; **50**: 719-25.
8. Nijhof SL, Priesterbach LP, Uiterwaal CSPM, Bleijenberg G, Kimpen JLL, van de Putte EM. Internet-Based Therapy for Adolescents With Chronic Fatigue Syndrome: Long-term Follow-up. *Pediatrics*. 2013; **131**: e1788-e1795.
9. White PD, Sharpe M, Chalder T, DeCesare JC, Walwyn R. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised

specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMCNeurol*. 2007; **7**: 6.

10. Sharpe MC, Archard LC, Banatvala JE, et al. A report--chronic fatigue syndrome: guidelines for research. *J R Soc Med*. 1991; **84**: 118-21.
11. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *J Psychosom Res*. 1993; **37**: 147-53.
12. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey. *Med Care*. 1992; **30**: 473-81.
13. Guy W. Clinical Drug evaluation (ECDEU) Assessment Manual. Rockville: National Institute of Mental Health; 1976.
14. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *The British journal of psychiatry : the journal of mental science*. 2002; **180**: 461-4.
15. Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMCHealth ServRes*. 2003; **3**: 25.
16. Tyrrell D. The London criteria. Report on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS) and myalgic encephalomyelitis (ME). Bristol: Westcare; 1994.
17. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders: Biometrics Research, New York State Psychiatric Institute, USA; 1999.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, D.C.: American Psychiatric Association; 1994.
19. Bonner D, Ron M, Chalder T, Wessely S. Chronic fatigue syndrome: a follow up study. *J Neurol Neurosurg Psychiatry*. 1994; **57**: 617-21.

FIGURES AND TABLES

Figure 1. Participation in the long-term follow-up study

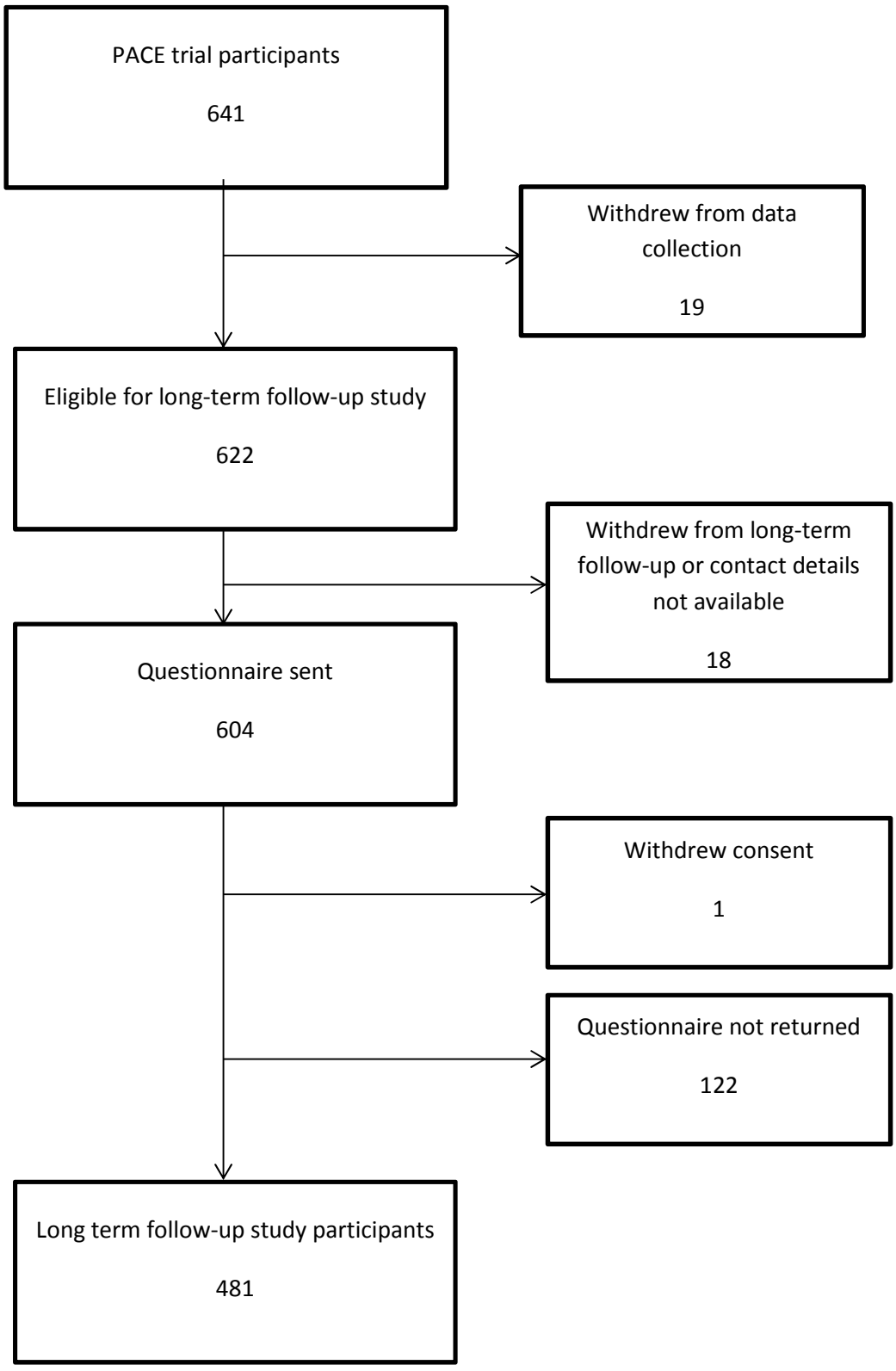
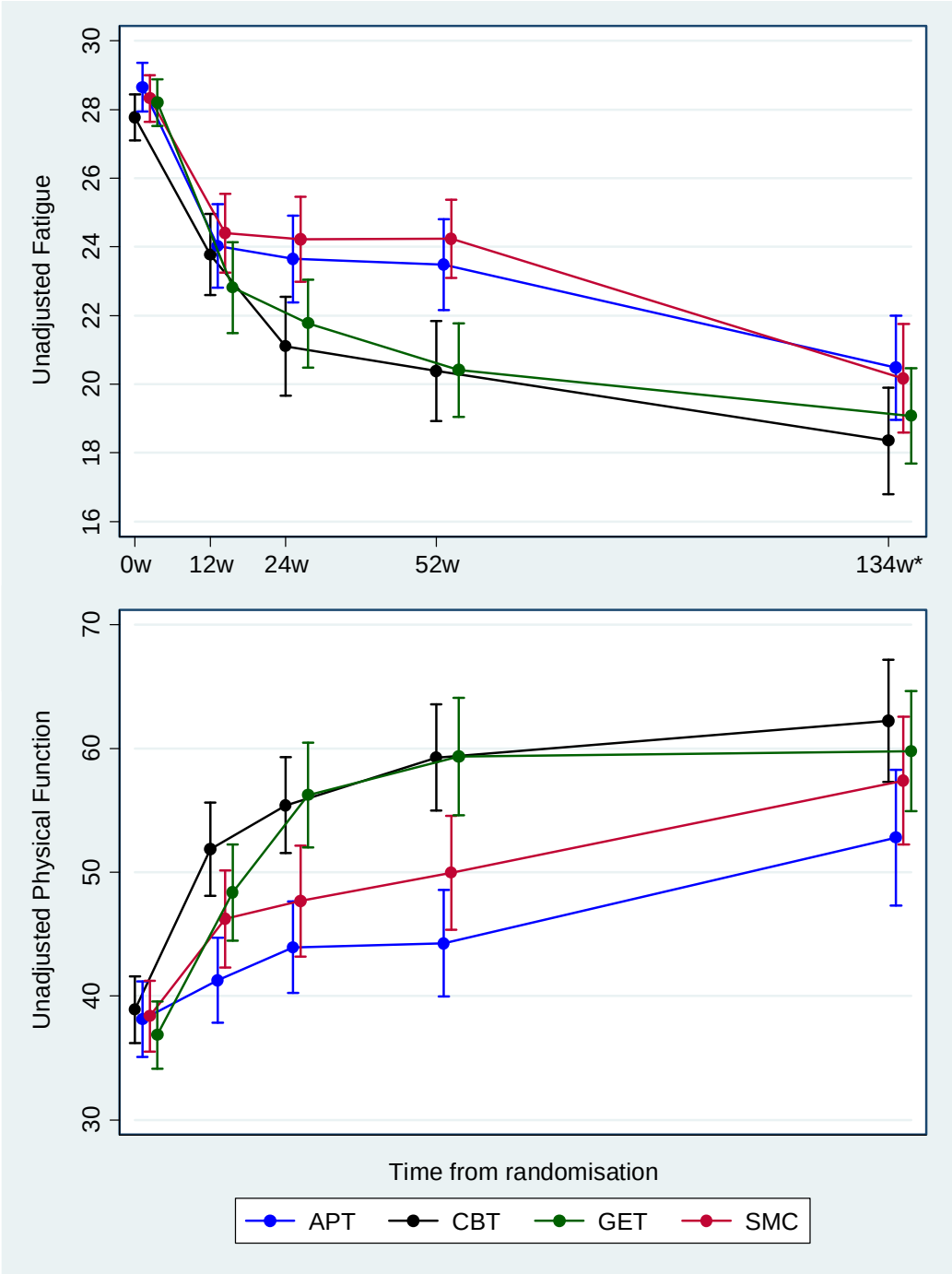


Figure 2. Unadjusted mean profile plots of fatigue and physical functioning by randomised treatment group for participants in the long-term follow-up study



Data are unadjusted means and 95% confidence intervals for the main trial time points (0, 12, 24, and 52 weeks post-randomisation) and long-term follow-up (*median 134 weeks).
w = weeks, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care

Table 1. Baseline characteristics of PACE trial participants who did and did not take part in the follow-up study

	Participated n=481	Did not participate n=159*	p-value**
Age (years)	38.6 (12.0)	37.5 (11.4)	0.33
Female sex	366 (76)	129 (81)	0.23
White ethnicity	451 (94)	144 (92)	0.45
CFS/ME patient group membership			0.015
Local self-help group for CFS/ME only	30 (6)	3 (2)	
National CFS/ME patient organization only	46 (10)	8 (5)	
Both	11 (2)	7 (4)	
None	394 (82)	141 (89)	
International criteria for CFS met	319 (66)	108 (68)	0.71
London criteria for ME met	252 (52)	77 (48)	0.41
Depressive disorder	152 (32)	61 (38)	0.12
Any psychiatric disorder	220 (46)	80 (50)	0.36
Duration of CFS (months)	32 (16, 66)	30 (18, 76)	0.90
Body Mass Index	25.3 (4.8)	25.9 (5.4)	0.20

Data are mean (SD), n (%) or median (25^{th} percentile, 75^{th} percentile).
CFS = chronic fatigue syndrome, ME = myalgic encephalomyelitis

* One trial participant withdrew consent for any use of their data after completion of the trial and did not return a long-term follow-up questionnaire.
**Fisher's exact test (categorical variables), independent samples t-test (continuous variables) or Mann-Whitney U test (illness duration) p-value for difference across treatment groups.

Table 2. Additional treatment received after final 12 month (52 week) trial outcome assessment

	All follow-up study participants n = 481	SMC n = 115	APT n = 120	CBT n = 119	GET n = 127	p-value**
Number (%) of participants who received any additional sessions*	210 (44)	73 (63)	60 (50)	36 (31)	41 (32)	<0.001
Median (quartiles) number of additional sessions received	0 (0, 8)	6 (0, 12)	1 (0, 8)	0 (0, 3)	0 (0, 6)	<0.001
Number (%) of participants who received an adequate number (10 or more) sessions of therapy						
received APT	15 (3)	6 (5)	0	2 (2)	7 (6)	0.016
received CBT	65 (14)	23 (20)	20 (17)	2 (2)	20 (16)	< 0.001
received GET	26 (5)	14 (12)	7 (6)	5 (4)	0	< 0.001

Data are n (%) or median (25^{th} percentile, 75^{th} percentile).
APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care alone

*Two participants indicated that they had additional sessions of a single type of therapy but the number of sessions received was missing; one was in the CBT group and had additional GET and the other was in the APT group and had additional APT.
**Fisher's exact test p-value for difference between treatment groups, except for number of additional sessions of therapy which is a Kruskal-Wallis test p-value.

Table 3. Summary statistics and within-group comparisons of long-term follow-up and final trial outcome assessment of PACE trial participants

	SMC	APT	CBT	GET
Fatigue (CFQ)				
Baseline n	160	159	161	160
Mean (SD)	28.3 (3.6)	28.5 (4.0)	27.7 (3.7)	28.2 (3.8)
52 weeks n	152	153	148	154
Mean (SD)	23.8 (6.6)	23.1 (7.3)	20.3 (8.0)	20.6 (7.5
Long-term n	115	120	119	127
Mean (SD)	20.2 (8.6)	20.5 (8.4)	18.4 (8.5)	19.1 (7.9)
Comparison n	114	119	118	127
Mean difference (CI)	-3.9 (-5.3, -2.6)	-3.0 (-4.4, -1.6)	-2.2 (-3.7, -0.6)	-1.3 (-2.7, 0.1)
	p < 0.001	p < 0.001	p = 0.006	p = 0.059
Physical functioning (SF-36PF)				
Baseline n	160	159	161	160
Mean (SD)	39.2 (15.4)	37.2 (16.9)	39.0 (15.3)	36.7 (15.4)
52 weeks n	152	153	148	154
Mean (SD)	50.8 (24.7)	45.9 (24.9)	58.2 (24.1)	57.7 (26.5)
Long-term* n	115	118	119	127
Mean (SD)	57.4 (27.9)	52.8 (30.2)	62.2 (27.2)	59.8 (27.6)
Comparison n	114	117	118	127
Mean difference (CI)	7.1 (4.0, 10.3)	8.5 (4.5, 12.5)	3.3 (0.02, 6.7)	0.5 (-2.7, 3.6)
	p < 0.001	p < 0.001	p = 0.049	p = 0.78
Overall change in perceived health (PGCI)				
52 weeks n	152	153	147	152
positive change n (%)	38 (25)	47 (31)	61 (42)	62 (41)
no change	100 (66)	96 (63)	77 (52)	80 (53)
negative change	14 (9)	10 (7)	9 (6)	10 (7)
Long-term n	115	118	119	127
positive change n (%)	48 (42)	45 (38)	50 (42)	61 (48)
no change	58 (50)	59 (50)	57 (48)	59 (47)
negative change	9 (8)	14 (12)	12 (10)	7 (6)
Comparison n	114	117	117	125
Difference in positive	18 (7, 28)	9 (-1, 18)	-3 (-11, 6)	2 (-7, 12)
change percentage (CI)	p = 0.001	p = 0.099	p = 0.68	p = 0.71
Difference in negative	-4 (-11, 4)	6 (-1, 13)	6 (-0.8, 13)	-2 (-7, 4)
change percentage (CI)	p = 0.42	p = 0.12	p = 0.092	p = 0.73
Impairment of daily activities (WSAS)				
Baseline n	160	158	161	160
Mean (SD)	26.9 (6.7)	27.9 (6.1)	27.4 (6.2)	26.8 (6.1)
52 weeks n	151	150	143	144
Mean (SD)	23.9 (9.2)	24.5 (8.8)	21.0 (9.6)	20.5 (9.4)
Long-term n	115	120	119	126
Mean (SD)	21.1 (11.5)	22.9 (11.7)	19.7 (10.2)	19.4 (10.8)
Comparison n	113	118	117	120
Mean difference (CI)	-3.2 (-4.7, -1.6)	-2.2 (-3.8, -0.6)	-0.9 (-2.2, 0.4)	-1.0 (-2.5, 0.4)
	p < 0.001	p = 0.007	p = 0.18	p = 0.16

All differences are between long term follow-up and 52 weeks. Mean differences and 95% confidence intervals for fatigue, physical functioning and work and social adjustment scale, difference in proportions with positive and negative change and 95% confidence intervals for overall

change in perceived health as compared to baseline. Lower scores are better for fatigue and work and social adjustment, higher scores are better for physical functioning. P-values for fatigue, physical functioning and work and social adjustment scale from paired samples t-tests; p-values for patient rated clinical global impression from McNemar test.

APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care alone, CFQ = Chalder Fatigue Questionnaire, SD = standard deviation, SF-36PF = SF-36 physical functioning subscale, WSAS =Work and Social Adjustment Scale, PGCI =participant-rated clinical global impression of change score. CI = confidence interval

*Two participants left the entire SF36 PF questionnaire blank at long-term follow-up and so were missing the physical functioning outcome measure.

WEB APPENDIX

Table A. Baseline characteristics of follow-up study participants by randomised treatment group

	SMC n=115	APT n=120	CBT n=119	GET n=127	p-value*
Age (years)	37.3 (11.3)	38.3 (11.5)	39.8 (12.1)	38.8 (13.1)	0.47
Female sex	82 (71)	94 (78)	95 (80)	95 (75)	0.43
White ethnicity	109 (96)	111 (93)	112 (94)	119 (94)	0.89
CFS/ME patient group membership					0.59
None	98 (85)	94 (78)	97 (82)	105 (83)	
Local self-help group for CFS/ME only	4 (4)	9 (8)	7 (6)	10 (8)	
National CFS/ME patient organization only	10 (9)	15 (13)	13 (11)	8 (6)	
Both	3 (3)	2 (2)	2 (2)	4 (3)	
International criteria for CFS	75 (65)	83 (69)	76 (64)	85 (67)	0.84
London criteria for ME	61 (53)	60 (50)	62 (52)	69 (54)	0.92
Current depressive disorder	36 (31)	40 (33)	37 (31)	39 (31)	0.97
Any psychiatric comorbidity	52 (45)	58 (48)	55 (46)	55 (43)	0.89
Duration of CFS (months)	29 (15, 58)	32 (16, 67)	33 (15, 105)	33 (16, 63)	0.44
BMI	25.1 (4.6)	25.2 (5.2)	25.3 (5.1)	25.6 (4.3)	0.84

Data are n (%), mean (SD), median (25^{th} percentile, 75^{th} percentile).
SMC = Standard medical care alone, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, CFS = chronic fatigue syndrome, ME = myalgic encephalomyelitis, BMI = body mass index

*Fisher's exact test (categorical variables), ANOVA (continuous variables), or Kruskal-Wallis test (illness duration) p-value for difference across treatment groups.

Table B. Number of additional therapy received after final 12 month (52 week) trial outcome assessment

	Original randomised treatment group				
Additional sessions	SMC n=115	APT n=120	CBT n=119	GET n=127	Overall n = 481*
SMC sessions					
None	94 (82)	101 (84)	101 (85)	111 (87)	407 (85)
1 to 4	12 (10)	17 (14)	14 (12)	15 (12)	58 (12)
5 to 9	7 (6)	1 (1)	4 (3)	1 (1)	13 (3)
10 or more	2 (2)	1 (1)	0	0	3 (1)
APT sessions					
None	102 (89)	114 (96)	111 (93)	116 (91)	443 (92)
1 to 4	0	3 (3)	4 (3)	0	7 (2)
5 to 9	7 (6)	2 (2)	2 (2)	4 (3)	15 (3)
10 or more	6 (5)	0	2 (2)	7 (6)	15 (3)
CBT sessions					
None	75 (65)	81 (68)	109 (92)	98 (77)	363 (76)
1 to 4	3 (3)	11 (9)	4 (3)	3 (2)	21 (4)
5 to 9	14 (12)	8 (7)	4 (3)	6 (5)	32 (7)
10 or more	23 (20)	20 (17)	2 (2)	20 (16)	65 (14)
GET sessions					
None	84 (73)	97 (81)	95 (81)	123 (97)	399 (83)
1 to 4	8 (7)	7 (6)	6 (5)	2 (2)	23 (5)
5 to 9	9 (8)	9 (8)	12 (10)	2 (2)	32 (7)
10 or more	14 (12)	7 (6)	5 (4)	0	26 (5)

Data are n (%).
SMC = specialist medical care alone, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy,

*Two participants indicated that they had additional sessions of a single type of therapy but data on the number of sessions were missing; one was in the CBT group and had additional GET and the other was in the APT group and had additional APT.

Table C. Differences in outcomes between originally randomised treatment groups*

	APT	CBT	GET
Fatigue (CFQ)			
Compared with SMC	0.3 (-1.7, 2.3)	-1.4 (-3.4, 0.7)	-0.8 (-2.8, 1.2)
P	0.78	0.19	0.43
Compared with APT		-1.6 (-3.6, 0.3)	-1.1 (-3.0, 0.9)
P	--	0.11	0.28
Physical function (SF-36PF)			
Compared with SMC	-3.6 (-9.6, 2.4)	2.8 (-3.2, 8.8)	2.0 (-4.0, 7.9)
P	0.24	0.36	0.51
Compared with APT		6.4 (0.4, 12.4)	5.6 (-0.3, 11.5)
P	--	0.035	0.064
Overall change in perceived health (PGCI)			
Compared with SMC	0.8 (0.4, 1.3)	0.9 (0.5, 1.5)	1.1 (0.6, 1.8)
P	0.32	0.62	0.85
Compared with APT		1.2 (0.7, 2.0)	1.4 (0.8, 2.3)
P	--	0.59	0.22
Impairment of daily activities (WSAS)			
Compared with SMC	1.3 (-1.2, 3.7)	-1.1 (-3.6, 1.4)	-0.8 (-3.2, 1.6)
P	0.30	0.38	0.51
Compared with APT		-2.4 (-4.8, 0.1)	-2.1 (-4.5, 0.3)
P	--	0.06	0.09

Mean differences between specified groups and 95% confidence intervals for fatigue, physical function, and work and social adjustment obtained from linear mixed effects models. Odds ratios for comparisons to specified group and 95% confidence intervals for overall change in perceived health obtained from generalized estimating equation models comparing positive change to no/negative change. Differences of negative magnitude for fatigue and work and social adjustment are favoured as the direction of these scales is lower is better, differences of positive magnitude for physical function are favoured as the direction of this scale is higher is better. For overall change in perceived health, odds ratios of greater than 1 are favoured, as the proportion with positive change is being compared.

APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, CFQ = Chalder Fatigue Questionnaire, SMC = specialist medical care, SF-36PF = SF-36 physical function subscale, PGCI =participant-rated clinical global impression of change score, WSAS =Work and Social Adjustment Scale.

*There is no column for SMC as this was only used as a comparison group